anoxic, not epileptic." Gastaut and Gastaut[9] induced 10 frank anoxic seizures[18] by ocular compression in 44 children with FCs but were unable to induce anoxic seizures in 66 children with symptoms of a cerebral lesion. Gastaut *et al*,[19] summarising the discussion and conclusions of the 1959 International Colloquium on Cerebral Anoxia and the EEG, said "two-thirds of attacks of unconsciousness in infancy (which are called 'convulsions') are in reality syncope due to cerebral ischaemia brought about by cardio-inhibitory reflexes." More recently, however, Gastaut[6] proposed that most FCs were epileptic,[20] with a familial predisposition. Evidence from the present study suggests that the anoxic mechanism is at least as important as an epileptic one in FCs, particularly since, because of hospital referral policy, epileptic FCs were over-represented in this study.

Numerous trials of antiepileptic drugs are now being carried out throughout the world on children with FCs. It is difficult to see how useful conclusions can be reached unless the investigators attempt to differentiate between anoxic and epileptic FCs and consider the interactions between each of these mechanisms and any preceding neurological abnormality in the child.[7]

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Sampling pure fetal blood by fetoscopy in second trimester of pregnancy

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Summary and conclusions

A technique for fetal blood-sampling in the second trimester of pregnancy (between 16 and 22 weeks' gestation) combining fetoscopy with real-time ultrasound was used in 48 attempts at fetal blood-sampling. Specimens containing fetal red cells with or without amniotic fluid or maternal blood, and adequate for diagnosing haemoglobinopathies, were obtained in 45 of the 48 fetoscopies. Sampling was successful in all 18 patients with a posterior placenta, and in 27 of the 30 with an anterior placenta. In 22 of the last 27 consecutive fetoscopies pure fetal blood was taken; the placenta was anterior in 16 and posterior in six. Out of 17 cases sampled between 18 and 22 weeks' gestation pure fetal blood was obtained in 16. The volume of the samples varied from 50 to 500 µl.

The ability to obtain pure fetal blood consistently even when the placenta is anterior will increase knowledge of fetal physiology and the scope of prenatal diagnosis.

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Introduction

Fetal red cells have been obtained in the second trimester by placentocentesis[1] and by fetoscopy.[2] The first technique can be used whatever the placental site, but the anterior placenta has hitherto been regarded as a contraindication to fetoscopy. The specimens obtained by either technique have usually consisted of a mixture of fetal and maternal blood or amniotic fluid, or of all three, with fetoscopy yielding a higher proportion of fetal red cells. Such specimens are adequate for prenatal diagnosis of haemoglobinopathies, but greater reliability in obtaining whole fetal blood, and thus pure fetal serum, would widen the scope of fetal investigation to include biochemical abnormalities that cannot be diagnosed from an analysis of amniotic fluid or fetal red cells.

We found that fetal blood sampling by fetoscopy may be performed when the placenta is anterior, and that samples of pure fetal blood, uncontaminated by maternal blood or amniotic fluid, can be reliably obtained.

Patients and methods

Gestational age is checked by an ultrasound scan and the timing of the fetoscopy planned; for diagnosing a haemoglobinopathy, fetoscopies may be done after 16 weeks' gestation, but better fetal blood samples are obtained after 18 weeks. When it is important to obtain pure fetal blood—for example, in carriers of Duchenne's muscular dystrophy—the procedure should take place at 18-20 weeks. A

Needlescope (Dyonics, Inc) is used,[2] and this is inserted into the uterine cavity under real-time ultrasound guidance.[3]

The real-time scanner is used immediately before the fetoscopy to identify the fetal position, placental margins, and cord insertion. The entry point for the fetoscope is then carefully chosen to avoid damage to fetus and placenta and to permit optimal access to the chorionic plate. When the placenta covers the whole of the anterior uterine wall, gentle pressure on one side of the uterus displaces amniotic fluid to the opposite side and can rotate the contralateral side forward, thus permitting the fetoscope to be introduced lateral to the placental margin. If possible, a large vessel near the cord insertion that can be approached at an acute angle is selected. The 27-gauge blood-sampling needle, with a 1- or 2-ml syringe attached to its hub, is passed down the Hobbins cannula and the vessel is punctured under direct vision. If blood is not obtained on aspiration, the needle is rotated and then slowly withdrawn while aspiration is continued. On further withdrawal of the needle, a perivascular, extra-amniotic haematoma may form, and this is also aspirated. Finally, blood mixed with amniotic fluid is obtained after the needle tip has emerged from the vessel.[2]

Each sample is immediately analysed on a Coulter Channelyzer, which detects the difference in size between maternal and fetal red cells and in a few seconds determines whether the sample has been contaminated by maternal blood. Thus the procedure can be stopped as soon as a suitable sample has been obtained. We aim at limiting its duration to 30 minutes, and the average duration is 20 minutes. All specimens are later checked by the Kleihauer method.

Seventy-one fetoscopies were performed, and fetal blood sampling was attempted in 48 of them. Placentocentesis was not used. Seventeen were done for diagnostic reasons and 31 before termination of pregnancy by intra-amniotic instillation of prostaglandins; informed consent was given in these cases. The mean gestational age was 18·5 weeks (range 16-22 weeks).

Results

Table I summarises the results; we did not select the cases, and the earliest ones are included. The placental site was classified according to the position of the bulk of the placenta.

TABLE I—*Results of fetoscopic blood sampling*

Quality of samples	No of fetoscopies	No with anterior placenta	No with posterior placenta
Pure fetal blood	22	16*	6
Samples mixed with amniotic fluid (% fetal red cells):			
100	18	8	10
50-60	3	1	2
4-6	2	2*	0
0†	3	3	0
Total	48	30	18

*In two cases vision was obscured due to old blood from previous amniocentesis.
†Maternal blood only.

FETAL RED CELLS

Specimens containing fetal red cells with or without amniotic fluid or maternal blood and adequate for prenatal diagnosis of haemoglobinopathies were obtained in 45 out of 48 fetoscopies (94%). The success rate with posterior placentas was 100% (18/18) and with anterior placentas 90% (27/30). The three failures (maternal blood only) occurred in patients with anterior placentas, but they were among the earliest attempts before a real-time scanner and Coulter Channelyzer were used; they were not diagnostic cases. In 40 of the 48 fetoscopies (83%) samples were obtained without maternal blood contamination; in 18 the sample consisted of 100% fetal cells with some admixture of amniotic fluid, and in 22 the sample was pure fetal blood.

PURE FETAL BLOOD

Pure fetal blood was obtained in 22 of the last 27 consecutive fetoscopies (81%). The placenta was anterior in 16 and posterior in six. The volume of the samples varied from 50 to 500 μl. In five, pure fetal blood was not obtained; three were done at 16 weeks' gestation, one at 17 weeks, and one at 22 weeks, in which visualisation was extremely difficult because of intra-amniotic bleeding after an amniocentesis that had been performed two weeks before the fetoscopy. In the last 27 cases the procedure was performed before 17 completed weeks' gestation in 10, and between 18 and 22 weeks in 17. Pure fetal blood was obtained in 6 (60%) and in 16 (94%) respectively.

In judging whether a sample consisted of pure fetal blood, several criteria were applied: the tip of the needle had to be within the fetal blood vessel or in an extra-amniotic perivascular haematoma; maternal red cells were absent according to both the Counter Channelyzer and the Kleihauer test; the red-cell indices agreed with available data.[4] In 14 cases after aliquots of blood had been removed to perform the relevant biochemical investigations enough was left over to do some of the tests for fetal red-cell indices (table II). In one patient the pregnancy was terminated by hysterotomy; fetal blood was obtained at necropsy and the indices agreed closely with those of the fetoscopic samples taken in utero. None of the 17 diagnostic cases required a repeat fetoscopy because of sampling failure and no spontaneous abortion occurred after fetoscopy. In none of the pregnancies that were terminated (36) or delivered (5) did the fetus show signs of damage. In some of the placentas perivascular haematomas, 1-2 mm in diameter, were visible, but no other trauma was seen.

TABLE II—*Red-cell indices in 14 specimens of fetal blood obtained by fetoscopy. Values are means (and ranges)*

Red cell count (10^{12}/l)	2·80 (2·23-4·37)
Mean cell volume (fl)	128 (116-139)
Packed cell volume	0·33 (0·25-0·42)
Gestational age (weeks)	18·5 (16-22)

Discussion

The results show that pure fetal blood can be consistently obtained by fetoscopy in the second trimester and that the technique is highly successful in patients with an anterior placenta. Nevertheless, success depends on careful attention to detail. Timing is important, since pure fetal blood is more difficult to obtain before 18 weeks' gestation. In our last 27 cases pure fetal blood was obtained in six out of 10 fetoscopies (60%) performed before 17 completed weeks, whereas during and after 18 weeks this was achieved in 16 out of 17 (94%). The failure to aspirate pure fetal blood in one patient in the latter group was attributed to contamination of the amniotic fluid with old blood, which made it difficult to see clearly. This had been caused by perforation of the anterior placenta during an amniocentesis two weeks before the fetoscopy. For similar reasons we had to abandon two other fetoscopies which were being done to examine the fetus (these are therefore not included in the present series). This emphasises the need to perform amniocentesis under careful ultrasound control, so that penetration of the placenta is avoided, particularly if a fetoscopy may be indicated at a later stage. Vision also becomes obscured after 22 weeks' gestation, due to increasing turbidity of the amniotic fluid.

Scanning immediately before fetoscopy with a real-time ultrasound machine allows an insertion site to be selected for the fetoscope that both avoids damage to the placenta and fetus and permits access to the major fetal vessels on the chorionic plate. The tip of the needle is more likely to remain in the lumen if a large vessel is punctured obliquely at an acute angle; with a perpendicular approach, the needle can easily be pushed through into the intervillous space of the placenta—that is, the maternal circulation.

The risks of fetoscopy cannot yet be firmly stated. Subsequent abortion may occur in as few as 4% of cases.[5] Fetal haemorrhage is unlikely to be serious,[2] particularly if the procedure is done after 18 weeks. If a perivascular haematoma has developed during the sampling, pressure from this may help to diminish blood loss. Bleeding usually stops after about 20 seconds. These risks compare favourably with those of placentocentesis, which may be associated with a fetal mortality of 10-12%.[6] Further-

more, the quality of the blood samples obtained by placentocentesis is inferior, and repeated attempts are more often necessary.

The red-cell values available at present[4] are based on old data; while ours (table II) are broadly similar, confirming that fetuses at this stage of pregnancy have a low red-cell count and packed cell volume and a high mean red-cell volume compared with adults, there are enough differences to suggest that further basic haematological information must be collected from fetoscopic samples. If pure fetal blood is consistently obtainable many physiological and pathological processes could be studied. We are currently investigating creatine phosphokinase[7] and factor VIII concentrations in fetal blood.

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Natural history and prognosis of recurrent breast cancer

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Summary and conclusions

Patterns of recurrent disease were analysed in 603 patients with breast cancer. The time of onset, frequency of recurrence, and survival after recurrence were not influenced by age or menopausal state. While survival after local recurrence was longer than survival after distant metastasis, the time to onset of local and distant disease followed an identical pattern, indicating that local recurrence should be regarded as a manifestation of systemic disease. Postoperative radiotherapy did not affect the time of onset of local recurrence.

We suggest that patients with local recurrence should receive both systemic and local treatment and that controlled trials of chemotherapeutic agents in these patients might be valuable in finding the most effective drug combinations to be used as adjuvant treatment after mastectomy.

Introduction

The survival of patients with cancer of the breast has not improved greatly in recent years.[1-3] Many carefully controlled trials of different methods of treatment have been carried out,[4-7] yet the results have shown remarkably little variation in the interval before metastases appear, or in survival, whatever the primary treatment. While a great deal of information is available on the management of so-called early breast cancer, little is known about the prognostic importance of different patterns of recurrent disease. Some patients with "local" recurrence have no evidence of distant metastases clinically or on investigation, yet many clinicians believe that local recurrence is a manifestation of systemic disease.[8-10] It is not clear, however, whether systemic treatment should be used in patients with locally recurrent disease.

There have been suggestions that postoperative radiotherapy may enhance dissemination of the tumour, but there is little information on the influence of radiotherapy on survival after metastases. The effect of menopausal state on the prognosis of recurrent disease is also poorly documented, as is the relation between the site of the primary tumour in the breast and the time of appearance of metastases. We therefore analysed in detail many patients with breast cancer treated in this hospital and tried to find out whether local and distant recurrences occur at similar times after primary treatment; postoperative radiotherapy delays the onset of local recurrence or influences survival once metastases have occurred; survival is different after local or distant metastasis; and menopausal state and age influence the time of onset of recurrence and survival after recurrence.

Patients and methods

During 1968-76, 603 patients with histologically proved adenocarcinoma of the breast were treated in this hospital; of these, 503 underwent simple mastectomy, 34 radical mastectomy, and 56 excision of the lump followed by radiotherapy. At the time there was a change from treatment by radical mastectomy in favour of local mastectomy followed by radiotherapy because it had been clearly shown that whereas there was little difference in survival with these two procedures, the morbidity associated with local mastectomy was less. Treatment policy was not standard, however, and some patients were selected for local excision because of variable criteria such as age or refusal to undergo mastectomy. Nevertheless, a general policy emerged, and most patients with medial tumours received radiotherapy, but many of those with lateral tumours and unaffected axillary nodes did not. Radiotherapy to the regional lymph nodes was given to all patients after operation if the axillary nodes were shown to be affected by cancer or if the tumour affected the medial half of the breast. The axilla and supraclavicular nodes received a total dose of 4500 rads over six weeks. In addition radiation to the chest wall after mastectomy or to the residual breast after excision of the lump was carried out in over 90% of patients who underwent postoperative

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